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Does A Balanced Transfusion Ratio of Plasma to Packed Red Blood Cells Improve Outcomes in Both Trauma and Surgical Patients? A Meta-Analysis of Randomized Controlled Trials and Observational Studies

Mohamed Rahouma[1] MD, Mohamed Kamel[1] MD, Diana Jodeh[1] MD, Thomas Kelley[2] MD, Lucas B Ohmes[1] MD, Andreas R de Biasi[1] MD, Ahmed Abouarab[1] MD, Umberto Benedetto[3] MD, PhD, T. Sloane Guy[1] MD, Christopher Lau[1] MD, Paul C. Lee[4] MD, MPH, Leonard N Girardi[1] MD, Mario Gaudino[1] MD, FECTS.

[1]*Department of Cardiothoracic Surgery, Weill Cornell Medicine, New York, NY*

[2]*Department of Surgery, Dwight D Eisenhower Army Medical Center, Augusta, GA*

[3]*Bristol Heart Institute, University of Bristol, School of Clinical Sciences, Bristol, United Kingdom*

[4] *Cardiothoracic Surgery, Northwell Health,* Hofstra Northwell School of Medicine, *New York, NY*

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Address for Correspondence:

Mario Gaudino, MD, Department of Cardiothoracic Surgery Weill Cornell Medicine

525 E 68th St, New York, New York 10065, USA Email: mfg9004@med.cornell.edu

Tel. +1 212 746 9440 Fax. +1 212 746 8080

Background:

Controversies persist regarding the effect of different transfusion ratios of fresh frozen plasma(FFP): packed red blood cell(RBC) on mortality. Observational evidence suggests a survival benefit for a high ratio in trauma patients, however, a recent, large, randomized controlled trial did not confirm this benefit. In recent years, the effect of this ratio has also been investigated in non-trauma settings. We herein offer an updated meta-analysis with the most recent literature and for the first time include a non-trauma cohort.

Methods:

A systematic review of balanced transfusion in trauma/on-trauma populations was conducted. Patients were categorized into high vs. low FFP:RBC ratio. Primary outcomes were 24-hour and 30-day/in-hospital mortality. Secondary outcomes were mortality differences in trauma vs non-trauma patients, mortality differences based on different transfusion ratio cutoffs (1:1, 1:1.5, or 1:2) and differences in acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) rates based on these ratios. Random model and leave-one-out-analyses were used.

Results:

36 studies with 16,607 patients were included; 34 traumas(16,027cases) and 2 non-trauma(580 cases; cardiac and vascular).
When pooling all studies together lower ratio was associated with poorer survival at 24-hr(OR=2.41;CI=1.94-3.01,p<0.001) and at 30-days (OR:1.74,CI=1.51-2.02,p<0.001).
In trauma settings, a lower ratio was associated with worse 24-hour and 30-day mortality(OR:2.41,CI=1.94-3.01,p<0.001 and OR:1.71,CI=1.47-1.98,p<0.001 respectively).
In non-trauma patients a lower ratio was associated with worse 30-day mortality(OR:2.60,CI =1.51-4.49,p<0.001).
In the entire cohort, a ratio of 1:1.5 provided the largest survival benefit at 24-hours and 30-days(OR:3.97,CI=1.37-11.49,p<0.001) and(OR:2.31,CI=1.17-4.57,p<0.001). There was no association between the ratio and ARDS or ALI.

Conclusions:

High FFP:RBC ratio confers both 24-hour and 30-day/in-hospital survival benefits, which were noted in trauma and non-trauma settings. A ratio of 1:1.5 was associated with the highest survival benefit.

Does A Balanced Transfusion Ratio of Plasma to Packed Red Blood Cells Improve Outcomes in Both Trauma and Surgical Patients? A Meta-Analysis of Randomized Controlled Trials and Observational Studies

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[1]Department of Cardiothoracic Surgery, Weill Cornell Medicine, New York, NY

[2]Department of Surgery, Dwight D Eisenhower Army Medical Center, Augusta, GA

[3]Bristol Heart Institute, University of Bristol, School of Clinical Sciences, Bristol, United Kingdom

[4] Cardiothoracic Surgery, Northwell Health, Hofstra Northwell School of Medicine, New York, NY

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Address for Correspondence:

Mario Gaudino, MD, Department of Cardiothoracic Surgery Weill Cornell Medicine

525 E 68th St, New York, New York 10065, USA Email: mfg9004@med.cornell.edu

Tel. +1 212 746 9440 Fax. +1 212 746 8080

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Methods:

A systematic review of the literature on balanced transfusion in both trauma and non-trauma populations was conducted. Patients were categorized into groups of high vs. low based on FFP: RBC ratio. Primary outcomes were 24-hour and 30-day/in-hospital mortality. Secondary outcomes were mortality differences in trauma vs non-trauma patients, mortality differences based on different transfusion ratio cutoffs (1:1, 1:1.5, or 1:2) and differences in acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) rates based on these ratios. Random model and leave-one-out-analyses were used.

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36 studies (2 RCTs, 34 observational) reporting outcomes on 16,607 patients were included; 34 traumas (16,027cases) and 2 non-trauma (580 cases; cardiac and vascular).
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Conclusions:

High FFP: RBC ratio confers both 24-hour and 30-day/in-hospital survival benefits, which were noted in trauma and non-trauma settings. A ratio of 1:1.5 was associated with the highest survival benefit.

Keywords:

24-hour and 30-day/in-hospital mortality; Fresh frozen plasma (FFP): packed red blood cell (RBC) ratio; Meta-analysis; Acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) rates

Introduction

The use of 1:1 balanced transfusion in massive traumatic hemorrhage has been an important topic over the past decade[1–4]. Until recently the primary method of resuscitation in massive hemorrhage was utilizing crystalloid and packed red blood cells (RBCs) and correcting coagulopathy as it arose. During the wars in Iraq and Afghanistan, the U.S. military utilize whole blood in austere situations for massive blood transfusion due to a rapidly available pool of donors. Initial studies on this transfusion method suggested that whole blood was as good as, and perhaps even superior to, traditional component transfusion practices with regards to coagulopathy in the setting of massive hemorrhage [5–7]. Other studies from civilian trauma suggested an advantage with early transfusion of FFP and platelets [8–10]. In a 2007 landmark retrospective study Borgman and colleagues [11] demonstrated that by attempting to recreate whole blood by balanced transfusion of individual blood products, mortality could be improved in a cohort of hemorrhaging patients in a combat setting. This and other small studies led to a directive within the U.S. military for a balanced, 1:1 ratio of blood products in massive transfusion when feasible.

Over the next several years, balanced transfusion was applied and studied throughout civilian trauma systems in numerous retrospective studies, yielding generally improved mortality when compared to unbalanced transfusion ratios. The practice remained controversial as the studies were retrospective and it was argued that many were subject to a survival bias since less severely injured patients were more likely to receive or achieve balanced transfusion[12]. This led to one prospective observational cohort study and one major randomized control trial (RCTs); The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) [13] study, and The Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients with Severe Trauma (PROPPRR) Trial [14]. The PROMMTT trial included patients who received a much lower number of blood products but still demonstrated increased survival with balanced transfusion early in the hospital course. Interestingly, the PROPPR trial did not demonstrate improved overall 24-hour or 30-day mortality but did demonstrate decreased mortality at 24 hours from exsanguination. There is very limited information regarding the effectiveness of balanced transfusion in other surgical specialties, likely because the transfusion practices for other surgical subspecialties are not standardized. The goal of this systematic analysis is to compare the effect of balanced, massive transfusion on mortality and secondary outcomes including acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) in a large, cohort of surgical patients, including both trauma and non-trauma sub specialties.

Methods

Study selection

A literature review using PubMed, MEDLINE, EMBASE, Web of Science, Science Direct, and Google scholar databases was performed by two independent investigators (MR and MK) up to January 10th, 2016. The following search terms were used:
(trauma OR traumatic OR injur* OR wound*) AND (massive OR major) AND (haemorrhag* OR hemorrhag* OR bleed* OR transfus* OR blood) AND (plasma OR component) AND (mortal* OR death* OR die OR died). Another search conducted by replacement of (trauma OR traumatic OR injur* OR wound*) by surgery in order to recruit non-trauma articles. In addition, upon identifying other meta-analyses or systematic reviews, references were scanned to capture relevant articles and pertinent reviews (i.e., backward snowballing). In case of disagreement a third investigator (MG) was included and an agreement was negotiated.

Study inclusion criteria

Studies included met the following criteria: (I) design was RCT or observational studies written in English, with more than 20 participants in each arm of the comparison; (II) massive blood transfused patients (all definitions accepted); (III) available mortality data based on the transfused FFP: RBC ratio; (IV) comparisons were made to contemporaneous patient cohorts, not to historical controls; (V) when cohorts overlapped between two studies, the more recent study was included.

Data extraction

Microsoft Office Excel 2010 (Microsoft, Redmond, Washington) was used for data extraction. Data extraction of all included studies was performed independently by 2 investigators (MR, DJ) and in case of disagreement a third investigator (MG) was included and an agreement was negotiated.
Extracted variables were: study name, publication year, study design, number of patients, sex, mean age, mean injury severity score (ISS), blunt injury percentage, military versus civilian environment, definition of massive transfusion, different FFP: RBC ratio categories, cut-off with different events number and total patients number in each group (then, categories were grouped as being low vs high for each study according to a predetermined ratios (1:1, 1:1.5, or 1:2) for analysis purposes), 24-hour mortality, 30-day/in-hospital mortality (if both were available, only in-hospital mortality data were used), morbidity outcomes (including ARDS and ALI), non-significant and significant differences between the different FFP: RBC ratio groups, factors associated with survival in the studied cohorts and lengths of hospital stay (LOS). The Newcastle-Ottawa Scale (NOS) was used to assess the quality of included studies [15]. Only high quality studies, defined as those achieving seven or more stars, were included in this review.

Study outcomes

Primary outcomes were 24-hr mortality and 30-day/in-hospital mortality for high vs low FFP: RBC ratio in the whole cohort while secondary outcomes were (I) mortality differences in trauma vs. non-trauma patients regarding FFP: RBC ratio, (II) mortality differences around the different cut-off ratios (1:1, 1:1.5, or 1:2) in order to identify the most beneficial ratio, and (III) ALI and ARDS differences between high vs. low ratios.

Statistical analysis

Review Manager Version 5.3 (RevMan) [16] was used to perform this pairwise meta-analysis, which was performed according to guidelines from the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group [17] and from the Preferred Reporting Items for Systematic reviews and Meta-Analysis group (PRISMA) [18]. The average of reported means of different studies was gathered for continuous variables.

The estimated survival data were obtained from the relevant articles either directly from published tables or indirectly from Kaplan–Meier curves using a previously described method [19] with aid of GetData Graph Digitizer software (http://getdata-graph-digitizer.com/).

Individual and pooled odds ratio (OR) with 95% confidence intervals (CI) were calculated by means of the DerSimonian-Laird (inverse variance [IV]) method [20]. OR was our measure for mortality as a dichotomous outcome with OR >1 indicating greater risk of an adverse event (i.e. death or complication as ARDS or ALI) happening in the low ratio group. P value <0.05 was used to indicate statistical significance.

Statistical heterogeneity was tested by the Cochran Q-test, with statistical significance set at the two-tailed 0.10 level, while extent of statistical consistency was measured with I^2 that equals to 100% X (Q-df)/Q; where Q is Cochran's heterogeneity statistic and df is the degrees of freedom.

The fixed-effect model was used in case of low statistical inconsistency ($I^2 \leq 25\%$) while random-effect model, that better accommodates clinical and statistical variations, in case of moderate or high statistical inconsistency ($I^2 > 25\%$). Higher values of I^2 signified increasing levels of heterogeneity between included studies with p-value <0.05 was considered evidence for significant heterogeneity. Publication bias was assessed by funnel plots. Subgroup analysis was performed based on whether studies were conducted in trauma versus non-trauma settings. Sensitivity analysis using leave-one-out analysis was performed by Comprehensive Meta-Analysis software, version 2 (Biostat, Englewood, NJ, USA).

Results

Included studies

Initially, 1,321 articles were identified through the PubMed search, with an additional 48 articles added through backward snowballing. Following review of titles and abstract, only 93 full text articles were assessed for final eligibility, among them only 36 studies (2 RCTs and 34 observational studies)[1–4,11,12,14,21–49] were included on the basis of our pre-defined inclusion/exclusion criteria (Figure 1). All but two retrospective studies [32,33], were from trauma settings.

Demographics of included studies

Total number of patients among the 34 trauma studies was 16,607 and of the 2 non-trauma (i.e. cardiac and vascular) articles was 580 patients. Twenty-eight studies were from civilian hospitals, 4 from military settings, and 4 from combined civilian/military settings. The majority of the included studies (31 studies) defined massive transfusion as 10 units of RBCs/24 hrs. Twenty-six articles were from the United States, 7 from Europe, 2 from Asia and 1 from Canada (Table 1).

The mean age was 39.1 years (range 23.5-73 years) for the entire cohort, while for trauma-only cases, the mean age was 37.1 years (range 23.5-47 years) versus 66.7 years (range 60.3-73 years) for non-trauma cases. Overall, 63% of trauma was blunt (range 3-100%), 23% of the population was female (range 2-39%), the average ISS was 31.99 (range 14.6-42.5), and the average baseline hemoglobin and platelets values were 10.60 g/dl and 189,100 µL respectively.

A total of 18/36 (50%) studies reported a FFP: RBC ratio ratio of 1:2 while 9 studies reported a ratio of 1:1 (Table 2). A ratio of 1:1.5 was reported in 6 articles and additional 3 studies reported their outcomes regarding various ratios (2:3 in 2 studies; and 1:2.3 in 1 study) (Figure 1).

Mortality

Short-term

24-hr morality was described by 22 studies, revealing higher mortality for lower ratios (OR 2.41, CI 1.94-3.01 p<0.001, Figure 2A & B) (9, 15–35), although at varying ratio cut-offs. Ratios of 1:2 were the most commonly reported, with 9 studies showing a deleterious effect with low ratio (OR: 2.85, CI 2.14-3.81). Seven articles reported a ratio of 1:1 (OR: 2.05, CI 1.55-2.71), and only 4 articles described a ratio of 1:1.5 (OR: 3.97, CI 1.37-11.49) (Table 3).

Intermediate-term

30-day/in-hospital mortality data were available from 27 studies (with different ratio cut-offs) and demonstrated higher mortality for lower ratios (OR: 1.74, CI 1.51-2.02, p<0.001, Figure 2C & D) (7, 9, 15, 18, 20–22, 25–29, 31–33, 36–47).

Ratios of 1:2 were the most commonly reported, with 14 studies showing a deleterious effect of ratio less than 1:2 versus higher ratio (OR: 1.77, CI 1.50-2.10, p<0.001). Seven articles reported a ratio of 1:1 (OR: 1.36, CI 1.09-1.69), while only five articles showed 1:1.5 ratios (OR: 2.31, CI 1.14-

5.25) which resulted in the highest OR among the various ratios. Figure 3 shows 24-hour and 30-day/in-hospital mortality at different ratios. Funnel plots were created to assess for publication bias. (Supplementary figure1)

Lower FFP: RBC ratio was associated with an increase in mortality rate among both trauma and non-trauma groups; however, this was more pronounced among non-trauma patients (OR: 2.60, CI 1.51-4.49 vs OR: 1.71, CI 1.47-1.98 for trauma cases), (Table 3, Supplementary figure 2)

Heterogeneity was evident among nearly all of outcomes, except for 30-day/in-hospital mortality for non-trauma studies (I^2=0%, P=0.32) and for ALI (I^2=0%, P=0.73; Table 3); thus, a random model was commonly adopted in this study.
Sensitivity studies using leave one out analysis of 24-hour and 30-day/in-hospital mortality at different ratios were done. (Supplementary figure 3)

Morbidity

ARDS data was available from 8 studies [2,14,28,29,35,40,45,46] and ALI data was reported in 2 studies [14,28]. There was no difference in the incidence of ARDS with respect to FFP: RBC ratio (OR: 0.68, CI 0.40-1.16, P=0.16). Similarly, no differences were observed in the incidence of ALI (OR: 1.23, CI 0.81-1.86, P=0.34). (Supplementary figure 4)

Discussion

The ideal ratio for balanced transfusion is a controversial issue with multiple facts and considerations ranging from patient outcomes to allocation of resources [1,50]. In their study Borgman and co-authors [11] found a higher transfusion ratio of 1:1.4 was significantly associated with improved mortality when compared to a medium (1:2.5) or low (1:8) ratios (19% vs 34% vs 65%, p<0.001, respectively). Recently, the Eastern Association for the Surgery of Trauma (EAST)[51] recommended damage control resuscitation (DCR) that entails transfusion of equal amounts of RBC, FFP, and PLT during the early, empiric phase of resuscitation as it can significantly improve the outcomes in severely injured bleeding patients. Civilian trauma centers around the world worked to create systems that could effectively transfuse quicker and at higher, more balanced ratios. The data that followed these changes was observational in nature. In general, the data from 2007 to 2015 supported balanced transfusion with a resultant improvement in the 24-hour and 30-day mortality rates. However, all of these studies were observational, which led to pleas for caution among many physicians. The main concern was that a paradigm shift was happening without high-quality evidence [52]. Many of these studies are limited by survival bias since the exact timing of blood products transfusion was often unknown. In addition, it is likely that ratios have had changed over time, introducing a length time bias. That is to say, the patients who have had survived were probably less injured, and thus, lived long enough to receive a balanced transfusion. Two smaller observational studies by Snyder et al. and Sperry et al. attempted to control for such survival bias, and are included in our analysis [12,40]. These authors examined blood product ratios as time varying covariates and were unable to demonstrate a survival benefit [12,40].

Noteworthy, many centers did not have an effective balanced transfusion protocol in place at the time of data collection. However, improving transfusion protocols (providing FFP in a timely manner) in many of these centers has resulted in a notable decline in mortality rates. These findings support the argument that by simply changing the transfusion protocol with a more readily available FFP, outcomes could improve as opposed to changing transfusion ratios.

Riskin et al[53] reported on the mortality rates of trauma patients 2 years before and 2 years after the implementation of a rapid massive transfusion protocol (MTP) at a level 1 trauma center. One of the main goals was to enhance communication with the blood bank to decrease time to first transfusion. Other implemented changes included having a designated MTP leadership and supporting a transfusion ratio of 1:1.5. They were able to demonstrate their hypothesis by implementing these changes, and without altering ratios, the mortality rate in massively bleeding patients dropped from 45% to 19%.

The first multicenter prospective observational cohort study, PROMMTT[13] in 2013 sought to describe the timing of blood products provision and assess the association between in-hospital mortality and the timing and amount of blood products given. This paper was not limited to massive transfusion as it was a feasibility study for a future, larger RCT. The authors found that the majority of patients did not reach a balanced transfusion ratio until about 3-6 hours into admission. One of the most important findings of this study was that early balanced transfusion led to a decreased 24-hour mortality; a finding seen previously by Borgman in 2007, and thus, a change in availability of non-balanced blood was not the only factor involved.

In 2015, Holcomb and colleagues published their widely anticipated data from the PROPPR RCT which examined 680 trauma patients who received early balanced massive transfusion. The goal of this study was to address the primary concerns raised in previous studies. All patients who met rather broad inclusion criteria received blood products within a preset time. The authors found that the effects of a 1:1:1 vs 1:1:2 (FFP:PLT:RBC) transfusion ratio had no difference in overall mortality at 24 hours (12.7% vs 17.0%, p=0.12) or at 30 days (22.4% vs 26.1%, p=0.26). The authors also pointed out that like many trauma trials, about one third of the deaths reported in the study were from traumatic brain injury, and thus, may have contributed to the failure to detect a significant difference in overall death rates [13]. Our results show that a higher transfusion ratio, no matter the definition, leads to improved survival in 24-hour and 30-day/in-hospital mortality. This is in line with the rational for an early 1:1:1 transfusion regimen which seeks to provide rapid hemorrhage control by replacing blood loss with products to recreate the actual composition of blood. In our study, the data supported the largest benefit for survival at 24 hours vs. 30 days (OR: 2.41, CI 1.94-3.01 vs. OR: 1.76, CI 1.51-2.05). It seems self-evident that the role of early balanced transfusion is most critical within the first hours of admission. As noted in PROMMTT and PROPPR study, after 24 hours is the time when other factors start to affect survival.

Unlike the present analysis, prior meta-analyses[54,55] did not include RCTs; in 2013 Bhangu et al[54] included six observational studies reporting the outcomes for 1,885 patients and reported a survival benefit with high FFP: RBC ratio without identifying additional benefits of 1:1 over 1:2 ratios. In 2011 Rajasekhar et al[55] published their meta-analysis of 11 observational studies that included 3,107 patients and found that there was an insufficient amount of evidence to support the survival advantage of a 1:1 ratio transfusion strategy. Our study is a large meta-analysis when compared with previous studies; including 36 articles, of which 2 are RTCs. The goal of this study was to look at mortality with relation to balanced transfusion among a broader range of surgical specialties. Of note, the goal of this paper was not to attempt to control for the inherent bias present in the observational studies. Instead, we wished to be as comprehensive as possible in regards to our inclusions. It is important that the readers understand that the primary source of our data is an observational trauma population. Articles about trauma represent the best evidence literature available regarding massive transfusions, and thus, would be the foundation of our study. The scarcity of balanced transfusion data among non-trauma patients highlights the need for a specific investigation in this area. Our study is the first to examine balanced transfusion in a non-trauma cohort. We investigated 2 studies comprising of 580 non-trauma patients and reported on mortality outcomes. We found that a lower transfusion ratio is associated with an increase in mortality among both groups, however, this was more pronounced among the non-trauma patients (OR: 2.60, CI 1.51-4.49 non-trauma vs OR: 1.71, CI 1.47-1.98 for trauma).

One of the concerns raised by opponents to national implementation of balanced transfusion was the possibility for a rise in transfusion associated injuries especially in massively transfused patients. Murad and colleagues, in a meta-analysis of 12,421 patients who received MTP, found that the transfusion of plasma was associated with a higher rate of ALI (OR: 3.00, CI, 1.29-4.75) in surgical patients alone[56] In the above mentioned randomized study and others the effect of transfusion ratio does not seem to influence the incidence of ARDS or ALI [14,35,45]. This aligns with our results showing that ARDS and ALI were not associated with different transfusion ratios.

The limitation of this study is that almost all of our data are observational, and thus, survival bias cannot be excluded. The authors did not try to adjust for this bias as it applied to almost all of the observational data papers. Due to the limited data on MTP in non-trauma patients, our study has a small sample size. This, however, highlights an area of future research and provides a corner stone for future reviews.

Conclusion

The use of high ratio, balanced transfusion will continue to be an important area of discussion and research. Our data suggests that there is a survival benefit at 24 hours and 30 days when this practice is followed, with the largest benefit within 24 hours. A ratio of 1:1.5 was associated with the highest survival benefit. Furthermore, there is no evidence in our study of increased rates of ALI or ARDS. Ultimately a larger prospective randomized controlled trial with several thousand patients will be required to determine the best ratio of blood products in massive transfusion.

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Table 1. Characteristics of included of included studies

Study	Year	Country	Centers	Study period	Type of study
Borgman (11)	2007	USA	Brooke Medical Army Center/Iraq	2003-2005	Retrospective
Borgman(1)	2011	Germany	Multi center	2002-2007	Retrospective
Brown(2)	2012	USA	Multi center	2003-2010	Prospective
Brown (21)	2011	USA	Multi center	2005-2006	Retrospective
De Biasi(3)	2011	USA	University of Maryland School of Medicine, Baltimore	2003-2008	Retrospective
Dente(4)	2009	USA	Multi center	2007-2008	Prospective
Duchesene(23)	2008	USA	Multi center	2002-2006	Retrospective
Duchesene(22)	2009	USA	Multi center	2001-2007	Retrospective
Gunter(24)	2008	USA	Multi center	2006-2007	Retrospective
Hardin(25)	2014	USA	Multi center	2003-2009	Retrospective
Holcomb(14)	2015	USA	Multi center	2012-2013	RCT
Holcomb(26)	2008	USA	Multi center	2005-2006	Retrospective
Kashuk (27)	2008	USA	Denver Health Medical Center	2001-2006	Retrospective
Kim (28)	2014	Korea	Ajou University School of Medicine	2010-2012	Retrospective
Lustenberger(29)	2011	Switzerland	University Hospital of Zurich	1996-2006	Retrospective
Maegele(30)	2008	Germany	Cologne-Merheim Medical Center	2002-2006	Retrospective
Magnotti(31)	2011	USA	University of Tennessee Health Science Center,Memphis	2006-2007	Retrospective
Mazzeffi(32)	2016	USA	University of Maryland School of Medicine	2006-2014	Retrospective
Mell(33)	2010	USA	University of Wisconsin	1987-2007	Retrospective
Mitra(34)	2010	Australia	Alfred Hospital	2004-2008	Retrospective
Nascimento(35)	2013	Canadian	Multi center	2009-2011	RCT
Peiniger(36)	2011	Germany	University of Witten	2002-2008	Retrospective
Rowell(37)	2011	USA	Multi center	2005-2007	Retrospective
Sharpe(38)	2012	USA	Multi center	2006-2009	Retrospective
Shaz(39)	2010	USA	Emory University Rollins School of Public Health, Atlanta, Georgia	2007-2009	Retrospective
Snyder(12)	2008	USA	University of Alabama-Birmingham (UAB) Hospital	2005-2007	Retrospective
Sperry(40)	2008	USA	Multi center	2003-2007	Prospective
Spinella(41)	2011	USA	Multi center	2005-2006	Retrospective
Spoerke(42)	2011	USA	Multi center	2005-2007	Retrospective

Stanworth(43)	2015	UK	Multi center	Till 2011	Prospective
Teixeira(44)	2009	USA	Multi center	2000-2005	Retrospective
Undurraga Peri(45)	2015	USA	Multi center	2012-2013	Retrospective
Van(46)	2010	USA	US army institute of surgical research	2003-2008	Retrospective
Wafaisade(47)	2011	Germany	University of Witten/Herdecke, Cologne-Merheim Medical Center	2005-2008	Retrospective
Yang (48)	2015	China	Medical College of Xi'an Jiaotong University	2009-2010	Retrospective
Zink(49)	2009	USA	Oregon Health & Science University	2005-2006	Retrospective

RCT: randomized control trial, USA: United States of America

Table 2. Patient details among FPR 1:2 included studies (n=18)

Author	Age	Females (%)	Military or Civilian	ISS	% Blunt injury	Exclusion criteria	Non-significant differences between groups	Significant differences between groups	Survival associated factors	Overall mean FU (mean or median)	NOS
Borgman (1)	42	33	Civilian	42.5	92	Death within 60 min of ED admission	Pressor-use, sepsis, single organ failure, MOF, vent-free days, ICU-free days, time to death	ICU LOS, in-hospital LOS, Mortality(6hr, 24hr, 30d and in-hospital)	Higher FPR	D/C	8/9
Brown(2)	40.5	27	Civilian	NR	100	None specified	Male, Mechanisum of injury, HR, RR, Temp, units of PRBCs transfused	age, GCS, PT, PTT, Plts, Hemoglobin, base deficit, systolic blood pressure, Units FFP transfused	24-h crystalloid, 24-h PRBC, Low hematocrit, No early laparotomy/thoracotomy, Initial BD, No 24-h vassopressor use, ISS , APACHE II	D/C	8/9
Dente (4)	36	17	Civilian	29	59	Non-trauma patients	24hrs and in-hospital mortality after penetrating trauma	24hrs and in-hospital mortality after blunt trauma	FPR in blunt trauma	D/C	8/9
Duchesene; (22)	30.25	11.25	Civilian	21.8	31.3	Patients < 18 years, who died in the ED, and nonsurvivable head injuries.	Age, Gender,SBP, ISS, Penetrating trauma, Initial(HB,BD, INR), operation time	ICU LOS, FPR	Higher FPR	D/C	9/9
Holcomb (26)	39.8	24.7	Civilian	32.3	65.8	Death within 30 minutes of ED admission	Gender, blunt trauma, admission HR, pH,Temp,Plt,ISS,AIS	Age, SBP,admission BD, INR, GCS	Higher FPR	30 days	9/9
Kashuk (27)	34.9	NR	Civilian	35.9	59	Severe head injury (1ry cause of death), ED resuscitative thoracotomy, documented severe comorbidities; COPD, CAD, CRF, and liver cirrhosis	NR	RBC transfused at 6 hours , INR at 6 hours 1.5 , ED temperature 34°C , and age 55 years.	FPR associated with coagulopathy reduction not survival	D/C	7/9
Kim (28)	47	17	Civilian	32	93	Death upon arrival to ED or within an hour	Age, gender, Blunt injury, Arrival-Transfusion (min), RBC-FFP transfusion (min), Colloid (L), Initial (hemoglobin, platelets, INR, pH,	Units PRBC/24 hr, Units FPR at 24 hr, Units platelets/24 hr, Crystalloids/24 hr (L), Initial DBP (mmHg)	Higher FPR	D/C	9/9

							lactic acid, base deficit), Initial (SBP HR, RR, temp, GCS).				
Magnotti (31)	38	31	Civilian	31.5	63	None specified	Age, ISS, gender, blunt trauma, admission (SBP, HR,INR, Plt)	Admission (BE, lactate)	Blunt injury, admission BE	D/C	8/9
Mazzeffi (32)	60.3	38.9	Civilian	NR	NR	None specified	Age, gender, weight, DM,Dyslipidemia, Hypertension, hemodialysis , baseline(creatinine, hematocrit, INR) , Infectious endocarditis, CLD, CHF, LVEF,ICU or hospital LOS	Hight,Baseline platelet count, PVD, prior MI, Warfain use, emergency operation, CPB time	Preoperative (platelet count, INR, thienopyridine) ,CPB time. Patients with a highFPR had improved 30-day survival	30 days/ D/C	8/9
Mell (33)	73	13.7	Civilian	NR	NR	Symptomatic patients but intact aneurysms, isolated iliac aneurysms, thoraco-abdominal aneurysms, death prior to operating room arrival	Age, weight, gender,hypertension, PVD, DM, Prior (MI, Stroke), operative time, blood loss, known AAA	COPD	Mortality higher in Age >80 ,Pre-operative tachycardia,Urine output, FFP: RBC <1:2	55 months	9/9
Peiniger (36)	42	16.7	Civilian	41.7	90	Death within the first hour after admission	Age, ISS, gender, blunt trauma, admission (SBP, HR, Plt, HB)	GCS, BE, MOF, sepsis	High FPR. RISC score	30 days	9/9
Rowell (37)	37.5	NR	Civilian	32	64.4	transferred patients from other hospitals, incarcerated, pregnant, < 16 years, burns, received CPR before ED, received ED thoracotomy, death within 30 minutes	ISS, GCS, BD, Age, AIS head, Temp	SBP (in penetrating trauma), HR(in blunt trauma), INR	Higher FPR	30 days	8/9
Shaz (39)	35	18	Civilian	27.7	53.5	Nontrauma patients	ISS, penetrating trauma, admission (HR, Temp, fibrinogen), GCS	Mortality (24 hours and 30 days)	Higher FPR	30 days	7/9
Snyder(12)	39.2	29	Civilian	36.5	100	None specified	NR	high survival with higher FPR	Higher FPR	30 days/ D/C	7/9
Spinella (41)	38	28.5	Military	35	100	Patients who died within the first hour of admission	Age, ISS, gender, blunt trauma, admission (SBP, HR, GCS, Plt)	BD	Higher FPR	30 days	8/9
Stanworth (43)	38	31	Civilian	28.5	77.4	Patients transferred from another hospital	Gender, blunt trauma, SBP	SBP on admission	Higher FPR	1 year	7/9

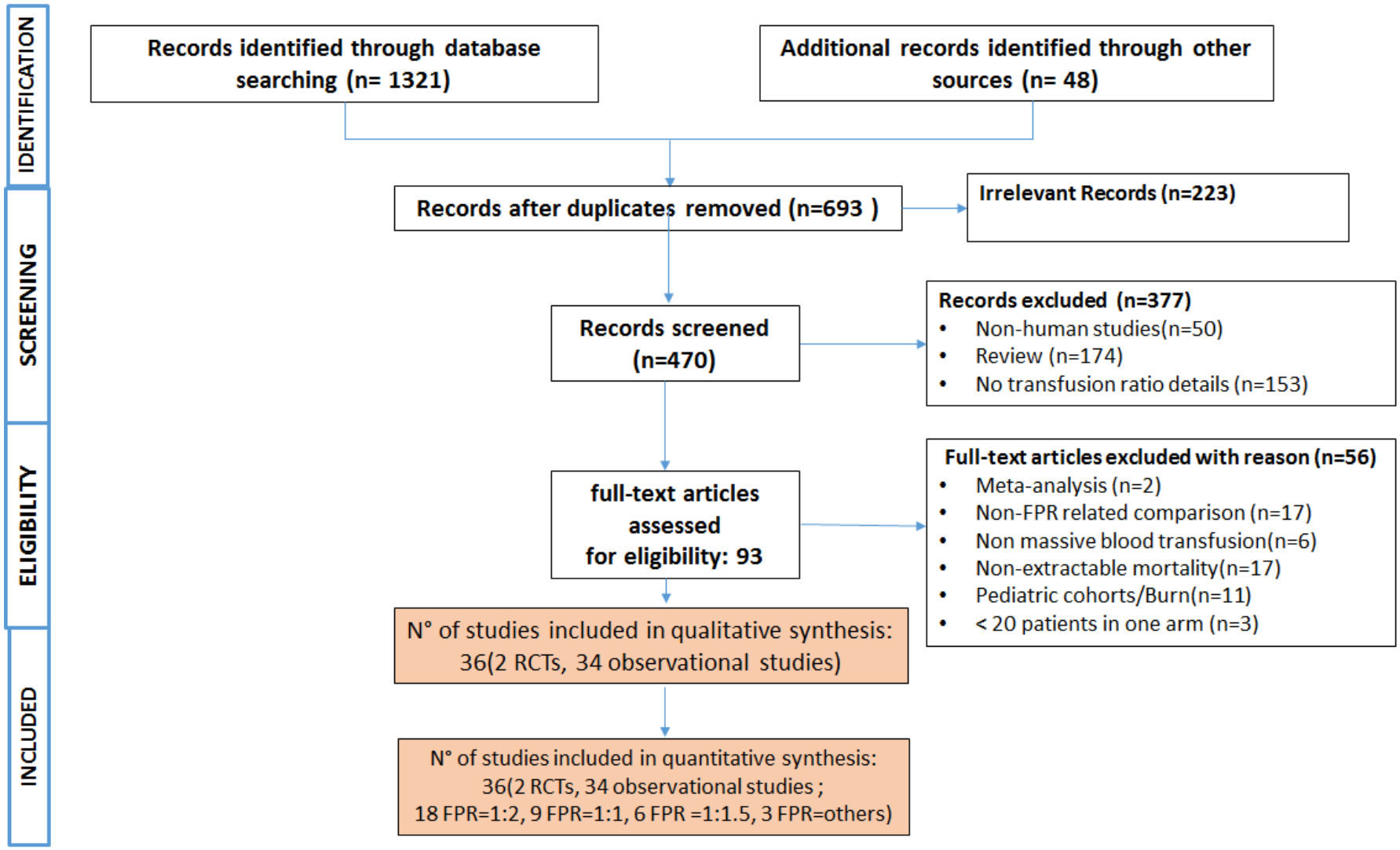
Teixeira (44)	32	13	Civilian	NR	NR	Head injury (AIS score of≥ 3)	NR	GCS 8, FPR, Abdominal AIS≥3, Age≥55, SBP<90, Vascular injury	Higher FPR	D/C	8/9
Van (46)	25.7	NR	Military	14.6	41	None specified	CVA, MI, ARDS,PE, DVT	Renal failure	Higher FPR	30 days	8/9

AAA; abdominal aortic aneurysm, AIS; abbreviated injury score, BD; base deficit, BE; base excess, CAD; coronary artery disease, CHF; congestive heart failure, CLD; chronic lung disease, CPB; cardio-pulmonary bypass, COPD; chronic obstructive pulmonary disease, CPR; cardiopulmonary resuscitation, CRF; chronic renal failure, CVA; cerebro-vascular accident, DVT; deep venous thrombosis, D/C; discharge, DM; diabetes mellitus, ED; Emergency department, FPR; fresh frozen plasma: packed red blood cells ratio ,GCS; Glasgow coma scale, HB; haemoglobin, HR; heart rate, ISS; injury severity score, LOS ; length of hospital stay, MBT; Massive blood transfusion, MI; myocardial infarction, MOF; multi-organ failure, NOS; Newcastle-Ottawa Scale, OEF; Operation Enduring Freedom, OIF; Operation Iraqi Freedom, PE; pulmonary embolus, Plt; platelets, PROPPR; The Pragmatic, Randomized Optimal Platelet and Plasma Ratios, PVD; peripheral vascular disease, RISC ; Revised Injury Severity Classification score, rFVIIa; recombinant factor VIIa , SBP; systolic blood pressure, TIC; traumatic induced coagulopathy

Table 3. All outcomes of interest

FPR	Outcome	Number of studies	Cases	OR	95% CI	Heterogeneity	Test for overall effect	Outcome higher in
All Studies (All Ratio; NO non-trauma)	24-hrs mortality	22	12178	2.41	1.94-3.01	*P*<0.00001, I^2=74%	Z=7.87, P=<0.00001	low ratio
All Ratio	In-hospital/ 30-day mortality	27	13075	1.74	1.51-2.02	P=0.0001, I2=57%	Z=7.44, P=<0.00001	low ratio
All Ratio (Trauma)	In-hospital/ 30-day mortality	25	12,495	1.71	1.47-1.98	*P*=0.0001, I^2=58%	*Z*=7.00, *P*=<0.00001	low ratio
All Ratio (Non-trauma)	In-hospital/ 30-day mortality	2	580	2.60	1.51-4.49	P=0.32, I^2=0%	*Z*=3.44, *P*=0.0006	low ratio
1:1	24-hrs mortality	7	5265	2.05	1.55-2.71	*P*=0.03, I^2=57%	*Z*=5.00, *P*=<0.00001	low ratio
1:1	In-hospital/ 30-day mortality	7	5266	1.36	1.09-1.69	P=0.09, I^2=45%	Z=2.74, P=<0.006	low ratio
1:1.5	24-hrs mortality	4	1877	3.97	1.37-11.49	*P*=<0.0001, I^2=88%	*Z*=2.55, *P*=<0.01	low ratio
1:1.5	In-hospital/ 30-day mortality	5	1813	2.31	1.14-5.25	P<0.001, I^2=84%	Z=2.40, P=0.02	low ratio
1:2	24-hrs mortality	9	3540	2.85	2.14-3.81	*P*=0.01, I^2=59%	*Z*=7.10, *P*=<0.00001	low ratio
1:2	In-hospital/ 30-day mortality	14	6193	1.77	1.50-2.10	*P*=0.08, I^2=37%	*Z*=6.68, *P*=<0.00001	low ratio
All Studies	ARDS	8	2678	0.68	0.40-1.16	*P*=0.0003, I^2=74%	*Z*=1.42, *P*=0.16	None
All Studies	ALI	2	780	1.23	0.81-1.86	*P*=0.73, I^2=0%	*Z*=0.96, *P*=0. 34	None

FPR; Fresh frozen plasma: packed RBCs ratio, CI, confidence interval; OR, odds ratio


IDENTIFICATION
SCREENING
ELIGIBILITY
INCLUDED
Records identified through database searching (n= 1321)
Additional records identified through other sources (n= 48)
Records after duplicates removed (n=693)
Irrelevant Records (n=223)
Records screened (n=470)
Records excluded (n=377)
• Non-human studies(n=50)
• Review (n=174)
• No transfusion ratio details (n=153)
full-text articles assessed for eligibility: 93
Full-text articles excluded with reason (n=56)
• Meta-analysis (n=2)
• Non-FPR related comparison (n=17)
• Non massive blood transfusion(n=6)
• Non-extractable mortality(n=17)
• Pediatric cohorts/Burn(n=11)
• < 20 patients in one arm (n=3)
N° of studies included in qualitative synthesis: 36(2 RCTs, 34 observational studies)
N° of studies included in quantitative synthesis: 36(2 RCTs, 34 observational studies ; 18 FPR=1:2, 9 FPR=1:1, 6 FPR =1:1.5, 3 FPR=others)

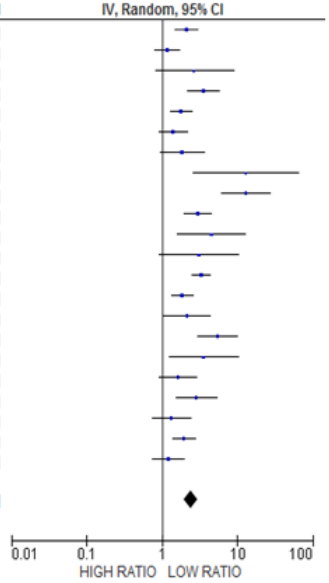
24 hrs Mortality

A)

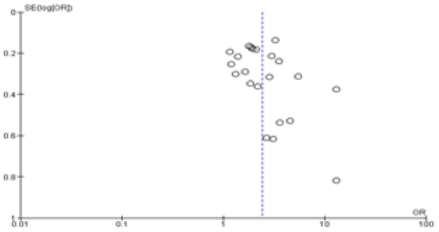
Study or Subgroup	LOW RATIO Events	Total	HIGH RATIO Events	Total	Weight	Odds Ratio IV, Random, 95% CI
Borgman 2011	83	237	86	422	5.9%	2.11 [1.47, 3.01]
de Biasi;2011	85	199	97	249	5.8%	1.17 [0.80, 1.71]
Dente 2009	7	23	7	50	2.3%	2.69 [0.81, 8.87]
Duchesene 2008	84	196	33	189	5.3%	3.55 [2.22, 5.67]
Hardin 2014	113	432	78	470	6.1%	1.78 [1.29, 2.46]
Holcomb 2015	58	342	43	338	5.6%	1.40 [0.91, 2.15]
Kashuk 2008	44	81	23	59	4.2%	1.86 [0.94, 3.68]
Kim 2014	9	32	2	68	1.5%	12.91 [2.60, 64.21]
Lustenberger 2011	31	52	18	177	3.9%	13.04 [6.23, 27.27]
Maegele 2008	158	484	32	229	5.6%	2.98 [1.96, 4.54]
Magnotti 2011	13	37	7	66	2.7%	4.57 [1.62, 12.84]
Mitra 2010	41	275	3	56	2.2%	3.10 [0.92, 10.38]
Peiniger 2011	159	379	157	871	6.4%	3.29 [2.52, 4.29]
Rowell 2011	128	375	71	328	6.0%	1.88 [1.34, 2.63]
Sharpe 2012	31	66	20	69	4.1%	2.17 [1.07, 4.41]
Shaz 2010	66	114	20	100	4.5%	5.50 [2.97, 10.17]
Sperry 2008	40	313	4	102	2.7%	3.59 [1.25, 10.29]
Spoerke 2011	222	1498	14	146	4.8%	1.64 [0.93, 2.90]
Stanworth 2015	26	92	25	206	4.5%	2.85 [1.54, 5.29]
Undurraga 2015	29	172	23	174	4.7%	1.33 [0.74, 2.41]
Wafaisade 2011	114	760	50	602	6.0%	1.95 [1.37, 2.77]
Yang 2015	22	186	86	862	5.2%	1.21 [0.74, 1.99]
Total (95% CI)		**6345**		**5833**	**100.0%**	**2.41 [1.94, 3.01]**
Total events	1563		899			

Heterogeneity: Tau² = 0.18; Chi² = 81.51, df = 21 (P < 0.00001); I² = 74%
Test for overall effect: Z = 7.87 (P < 0.00001)

Odds Ratio IV, Random, 95% CI



B)



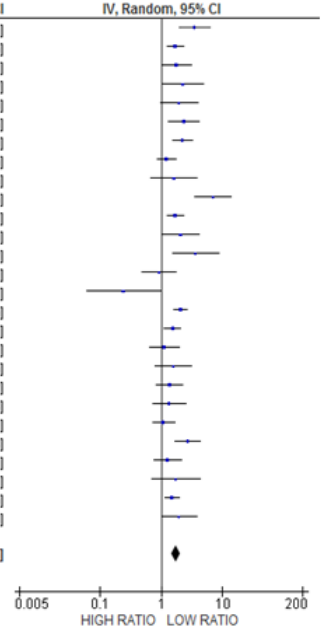
30days/ in-hospital mortality

C)

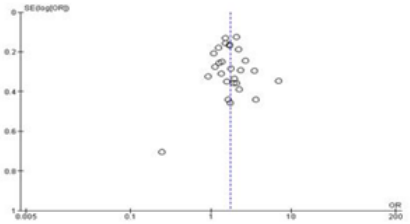
Study or Subgroup	LOW RATIO Events	Total	HIGH RATIO Events	Total	Weight	Odds Ratio IV, Random, 95% CI
Borgman 2007	38	84	31	162	3.4%	3.49 [1.95, 6.24]
Borgman 2011	113	237	147	422	5.5%	1.70 [1.23, 2.36]
Brown 2011	35	186	25	215	3.6%	1.76 [1.01, 3.07]
Brown 2012	68	476	8	116	2.5%	2.25 [1.05, 4.82]
Duchesene 2009	30	63	23	72	2.8%	1.94 [0.96, 3.90]
Gunter 2008	120	195	26	64	3.5%	2.34 [1.31, 4.16]
Holcomb 2008	128	214	103	256	5.0%	2.21 [1.53, 3.20]
Holcomb 2015	89	342	75	338	5.2%	1.23 [0.87, 1.75]
Kim 2014	14	32	22	68	2.1%	1.63 [0.69, 3.86]
Lustenberger 2011	36	52	43	177	2.8%	7.01 [3.55, 13.86]
Maegele 2008	222	484	76	229	5.4%	1.71 [1.23, 2.37]
Mazzeffi 2016	13	88	28	364	2.7%	2.08 [1.03, 4.20]
Mell 2010	16	41	13	87	2.1%	3.64 [1.54, 8.62]
Mitra 2010	16	56	83	275	3.1%	0.93 [0.49, 1.74]
Nascimento 2013	3	32	11	37	1.0%	0.24 [0.06, 0.97]
Peiniger 2011	206	379	317	871	6.2%	2.08 [1.63, 2.66]
Rowell 2011	167	375	113	328	5.6%	1.53 [1.13, 2.07]
Shaz 2010	50	114	41	100	3.7%	1.12 [0.65, 1.94]
Snyder 2008	43	74	28	60	2.8%	1.59 [0.80, 3.15]
Sperry 2008	110	313	29	102	4.1%	1.36 [0.84, 2.22]
Spinella 2011	22	185	25	276	3.3%	1.36 [0.74, 2.48]
Spoerke 2011	351	1498	32	146	4.7%	1.09 [0.72, 1.64]
Teixeira 2009	131	268	30	115	4.1%	2.71 [1.68, 4.38]
Undurraga 2015	43	172	36	174	4.0%	1.28 [0.77, 2.11]
Van 2010	10	88	11	159	2.0%	1.72 [0.70, 4.24]
Wafaisade 2011	205	760	118	602	6.1%	1.52 [1.17, 1.96]
Zink 2009	161	401	13	51	3.0%	1.96 [1.01, 3.80]
Total (95% CI)		**7209**		**5866**	**100.0%**	**1.74 [1.51, 2.02]**
Total events	2440		1507			

Heterogeneity: Tau² = 0.07; Chi² = 60.82, df = 26 (P = 0.0001); I² = 57%
Test for overall effect: Z = 7.44 (P < 0.00001)

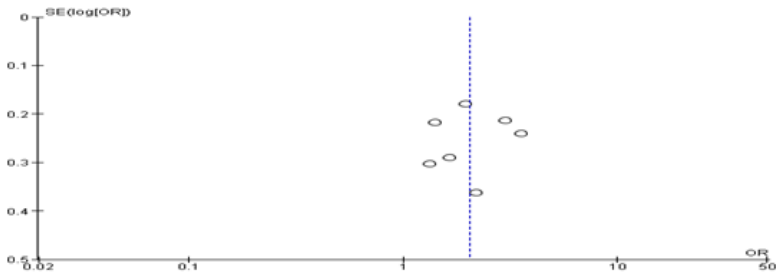
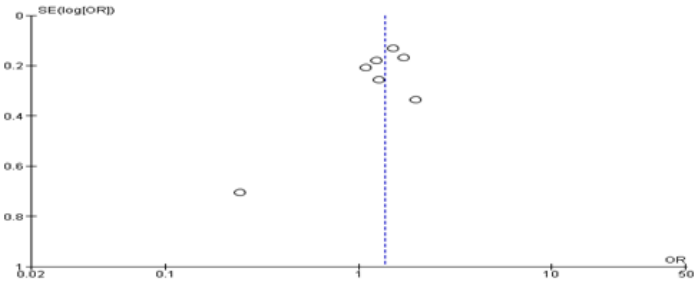
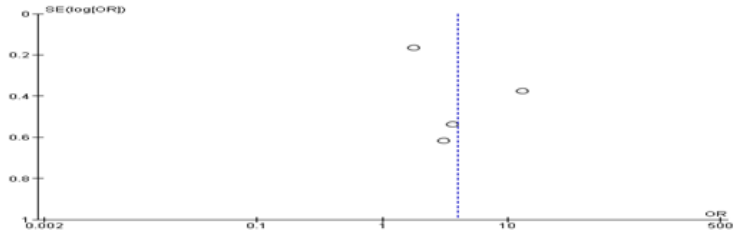
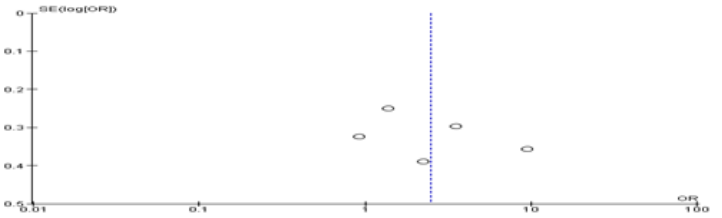
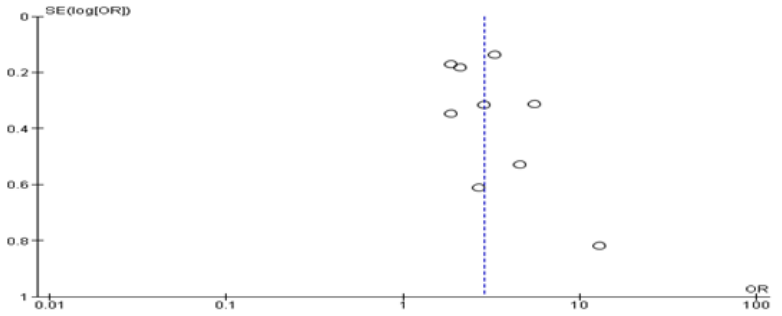
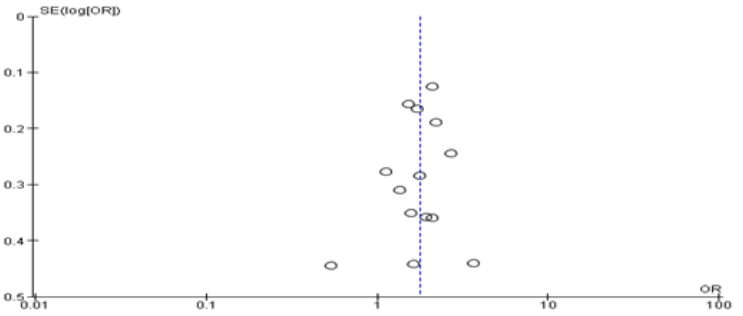
Odds Ratio IV, Random, 95% CI



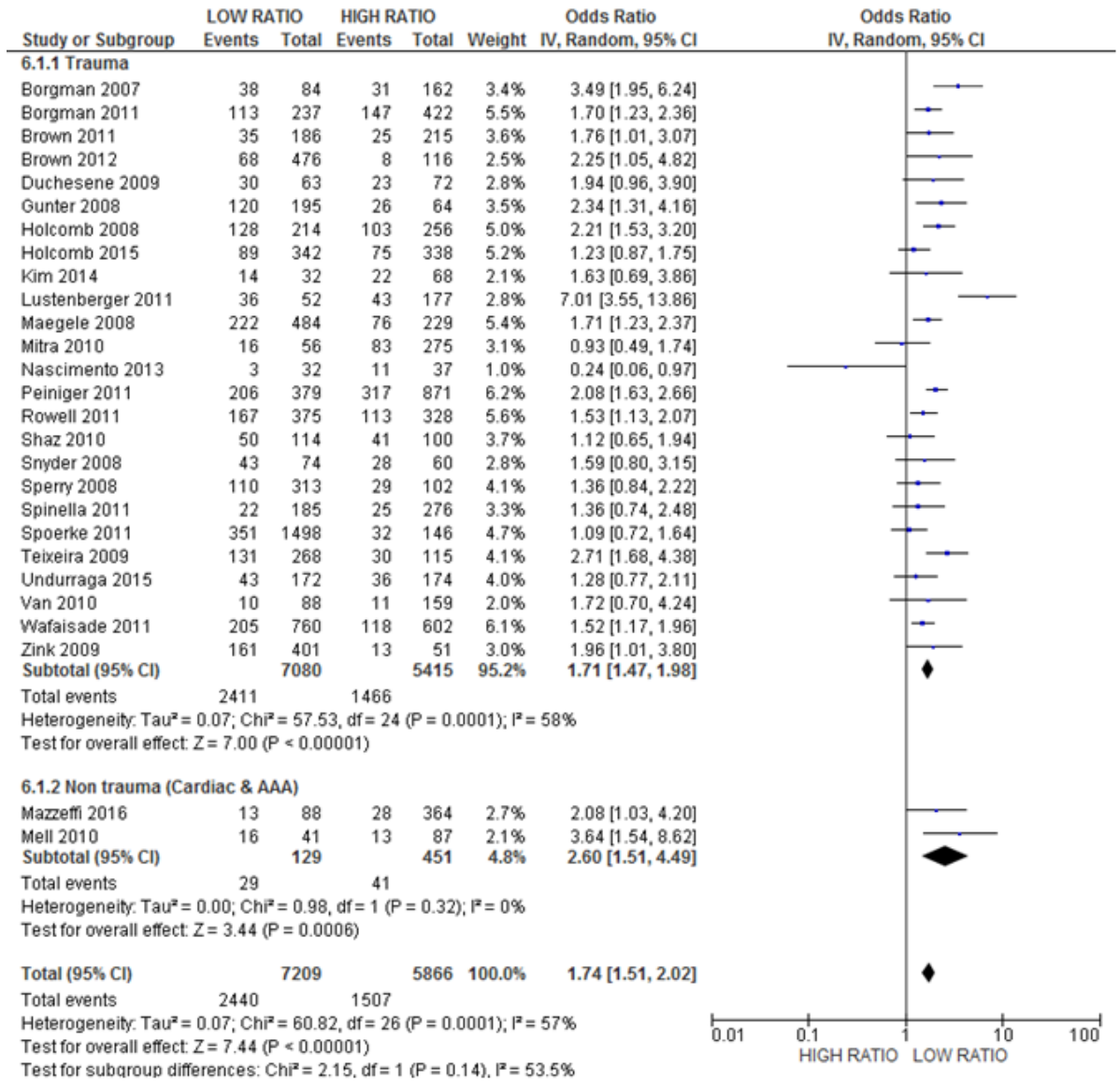
D)



	24 hrs. Mortality	30days/ in-hospital mortality
RATIO 1:1	**1A)** Low Ratio < 1:1 | High Ratio ≥ 1:1 | Odds Ratio | Odds Ratio Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI Duchesene 2009 84 196 33 189 14.9% 3.55 [2.22, 5.67] Holcomb 2015 58 342 43 338 16.1% 1.40 [0.91, 2.15] Maegele 2008 158 484 32 229 16.4% 2.98 [1.96, 4.54] Sharpe 2012 31 66 20 69 9.7% 2.17 [1.07, 4.41] Spoerke 2011 222 1498 14 146 12.5% 1.64 [0.93, 2.90] Undurraga 2015 29 172 23 174 12.0% 1.33 [0.74, 2.41] Wafaisade 2011 114 760 50 602 18.3% 1.95 [1.37, 2.77] Total (95% CI) 3518 1747 100.0% 2.05 [1.55, 2.71] Total events 696 215 Heterogeneity: Tau² = 0.08; Chi² = 14.07, df = 6 (P = 0.03); I² = 57% Test for overall effect: Z = 5.00 (P < 0.00001) 0.02 0.1 1 10 50 High Ratio ≥ 1:1 Low Ratio < 1:1	**1B)** Low Ratio < 1:1 | High Ratio ≥ 1:1 | Odds Ratio | Odds Ratio Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI Holcomb 2015 89 342 75 338 18.3% 1.23 [0.87, 1.75] Maegele 2008 222 484 76 229 19.5% 1.71 [1.23, 2.37] Nascimento 2013 3 32 11 37 2.3% 0.24 [0.06, 0.97] Spoerke 2011 351 1498 32 146 15.7% 1.09 [0.72, 1.64] Undurraga 2015 43 172 36 174 12.3% 1.28 [0.77, 2.11] Wafaisade 2011 205 760 118 602 23.5% 1.52 [1.17, 1.96] Zink 2009 161 401 13 51 8.4% 1.96 [1.01, 3.80] Total (95% CI) 3689 1577 100.0% 1.36 [1.09, 1.69] Total events 1074 361 Heterogeneity: Tau² = 0.04; Chi² = 10.93, df = 6 (P = 0.09); I² = 45% Test for overall effect: Z = 2.74 (P = 0.006) 0.02 0.1 1 10 50 High Ratio ≥ 1:1 Low Ratio < 1:1
RATIO 1:1.5	**2A)** Low Ratio < 1:1.5 | High Ratio ≥ 1:1.5 | Odds Ratio | Odds Ratio Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI Hardin 2014 113 432 78 470 29.1% 1.78 [1.29, 2.46] Lustenberger 2011 31 52 18 177 26.2% 13.04 [6.23, 27.27] Mitra 2010 41 275 3 56 21.6% 3.10 [0.92, 10.38] Sperry 2008 40 313 4 102 23.1% 3.59 [1.25, 10.29] Total (95% CI) 1072 805 100.0% 3.97 [1.37, 11.49] Total events 225 103 Heterogeneity: Tau² = 0.98; Chi² = 24.01, df = 3 (P < 0.0001); I² = 88% Test for overall effect: Z = 2.55 (P = 0.01) 0.002 0.1 1 10 500 High Ratio ≥ 1:1.5 Low Ratio < 1:1.5	**2B)** Low Ratio < 1:1.5 | High Ratio ≥ 1:1.5 | Odds Ratio | Odds Ratio Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI Borgman 2007 38 84 31 162 20.5% 3.49 [1.95, 6.24] Brown 2012 68 476 8 116 18.8% 2.25 [1.05, 4.82] Lustenberger 2011 36 52 34 177 19.4% 9.46 [4.71, 19.01] Mitra 2010 16 56 83 275 20.0% 0.93 [0.49, 1.74] Sperry 2008 110 313 29 102 21.2% 1.36 [0.84, 2.22] Total (95% CI) 981 832 100.0% 2.45 [1.14, 5.25] Total events 268 185 Heterogeneity: Tau² = 0.65; Chi² = 30.05, df = 4 (P < 0.00001); I² = 87% Test for overall effect: Z = 2.31 (P = 0.02) 0.01 0.1 1 10 100 High Ratio ≥ 1:1.5 Low Ratio < 1:1.5
RATIO 1:2	**3A)** Low Ratio <1:2 | High Ratio ≥ 1:2 | Odds Ratio | Odds Ratio Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI Borgman 2011 83 237 86 422 17.1% 2.11 [1.47, 3.01] Dente 2009 7 23 7 50 4.7% 2.69 [0.81, 8.87] Kashuk 2008 44 81 23 59 10.1% 1.86 [0.94, 3.68] Kim 2014 9 32 2 68 2.9% 12.91 [2.60, 64.21] Magnotti 2011 13 37 7 66 5.9% 4.57 [1.62, 12.84] Peiniger 2011 159 379 157 871 19.3% 3.29 [2.52, 4.29] Rowell 2011 128 375 71 328 17.5% 1.88 [1.34, 2.63] Shaz 2010 66 114 20 100 11.3% 5.50 [2.97, 10.17] Stanworth 2015 26 92 25 206 11.3% 2.85 [1.54, 5.29] Total (95% CI) 1370 2170 100.0% 2.85 [2.14, 3.81] Total events 535 398 Heterogeneity: Tau² = 0.09; Chi² = 19.35, df = 8 (P = 0.01); I² = 59% Test for overall effect: Z = 7.10 (P < 0.00001) 0.01 0.1 1 10 100 High Ratio ≥ 1:2 Low Ratio < 1:2	**3B)** Low Ratio < 1:2 | High Ratio ≥ 1:2 | Odds Ratio | Odds Ratio Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI Borgman 2011 113 237 147 422 12.0% 1.70 [1.23, 2.36] Brown 2011 35 186 25 215 6.4% 1.76 [1.01, 3.07] Duchesene 2009 30 63 23 72 4.5% 1.94 [0.96, 3.90] Holcomb 2008 128 214 103 256 10.6% 2.21 [1.53, 3.20] Kim 2014 14 32 22 68 3.2% 1.63 [0.69, 3.86] Mazzeffi 2016 13 88 28 364 4.5% 2.08 [1.03, 4.20] Mell 2010 16 41 13 87 3.2% 3.64 [1.54, 8.62] Peiniger 2011 206 379 317 871 14.9% 2.08 [1.63, 2.66] Rowell 2011 167 375 113 328 12.6% 1.53 [1.13, 2.07] Shaz 2010 50 114 41 100 6.6% 1.12 [0.65, 1.94] Snyder 2008 43 74 28 60 4.7% 1.59 [0.80, 3.15] Spinella 2011 22 185 25 276 5.7% 1.36 [0.74, 2.48] Teixeira 2009 131 268 30 115 7.8% 2.71 [1.68, 4.38] Van 2010 10 439 11 264 3.2% 0.54 [0.22, 1.28] Total (95% CI) 2695 3498 100.0% 1.77 [1.50, 2.10] Total events 978 926 Heterogeneity: Tau² = 0.03; Chi² = 20.66, df = 13 (P = 0.08); I² = 37% Test for overall effect: Z = 6.68 (P < 0.00001) 0.01 0.1 1 10 100 High Ratio ≥ 1:2 Low Ratio < 1:2

	24 hrs Mortality	30days/ in-hospital mortality
RATIO 1:1		
RATIO 1:1.5		
RATIO 1:2		

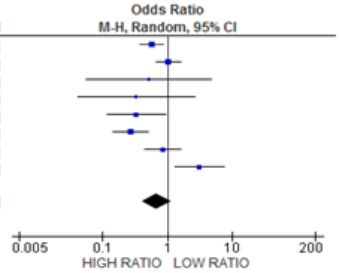
30days/ in-hospital mortality (Trauma vs non-trauma)

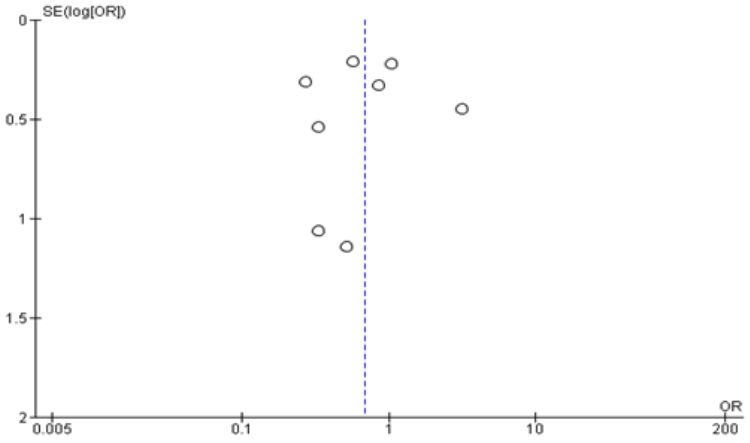


A) ARDS

Study or Subgroup	LOW RATIO Events	Total	HIGH RATIO Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Brown 2012	133	476	47	116	17.8%	0.57 [0.37, 0.87]
Holcomb 2015	48	342	46	338	17.7%	1.04 [0.67, 1.60]
Kim 2014	1	32	4	68	4.4%	0.52 [0.06, 4.81]
Lustenberger 2011	1	52	10	177	4.9%	0.33 [0.04, 2.62]
Nascimento 2013	7	32	17	37	11.2%	0.33 [0.11, 0.95]
Sperry 2008	24	313	24	102	15.8%	0.27 [0.15, 0.50]
Undurraga 2015	19	172	22	174	15.4%	0.86 [0.45, 1.65]
Van 2010	14	88	9	159	12.9%	3.15 [1.30, 7.62]
Total (95% CI)		**1507**		**1171**	**100.0%**	**0.68 [0.40, 1.16]**
Total events	247		179			

Heterogeneity: Tau² = 0.37; Chi² = 27.26, df = 7 (P = 0.0003); I² = 74%
Test for overall effect: Z = 1.42 (P = 0.16)





B) ALI

Study or Subgroup	LOW RATIO Events	Total	HIGH RATIO Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Kim 2014	0	32	1	68	2.4%	0.69 [0.03, 17.46]
Holcomb 2015	57	342	47	338	97.6%	1.24 [0.81, 1.88]
Total (95% CI)		**374**		**406**	**100.0%**	**1.23 [0.81, 1.86]**
Total events	57		48			

Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.96 (P = 0.34)